ACUTE TOXICITY SUMMARY

NITROGEN DIOXIDE

CAS Registry Number: 10102-44-0

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**470 μg/m³**
Critical effect(s)	increased airway reactivity in asthmatics
Hazard Index target(s)	Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid, reddish brown gas
Molecular formula	NO_2
Molecular weight	46.01
Density	1.448 g/cm^3 @ 20°C (liquid) 1.88 g/L @ 25°C (gas)
Boiling point	21.15° C (70°F)
Melting point	-9.3° C
Vapor pressure	720 mm Hg @ 20°C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	soluble in concentrated nitric and sulfuric acids; decomposes in water, forming nitric oxide and nitric acid.
Odor threshold	0.11-0.22 ppm
Odor description	similar to that of bleach (AIHA, 1989)
Metabolites	nitrogen dioxide and water combine to produce nitric acid in the respiratory tract
Conversion factor	1 ppm = 1.88 mg/m³ @ 20°C

III. Major Uses or Sources

Nitrogen dioxide (NO_2) is used as a nitrating agent, as a component of rocket fuels, and as an intermediate in the formation of nitric acid (ACGIH, 1986). The majority of occupational exposures to NO_2 result from its presence as a by-product of nitrate decomposition, as in the reaction of nitric acid with metals or other reducing agents, various processes in which air is heated to high temperature with the formation of nitric oxide (NO), or in the exhaust of internal-combustion engines.

Major indoor sources of NO_2 include unvented gas stoves, other gas appliances, and kerosene heaters (CARB, 1992). The major outdoor sources of NO_2 emissions in California are: on-road vehicles (approximately 51%), other vehicles, locomotives, aircraft (23%), and stationary combustion sources (e.g., oil and gas production, and refining, manufacturing/industrial, and electric utilities) (26%).

IV. Acute Toxicity to Humans

Acute exposure to NO_2 has caused pulmonary edema, pneumonitis, bronchitis, and bronchiolitis obliterans (Reprotext, 1999). NO_2 is considered a relatively insoluble, reactive gas, such as phosgene and ozone. Once inhaled, it reaches the lower respiratory tract, affecting mainly the bronchioles and the adjacent alveolar spaces, where it may produce pulmonary edema within hours (Plog, 1988). Many deaths from pulmonary edema have been induced by acute inhalation of high concentrations of NO_2. Short exposures to 100-500 ppm (190-900 mg/m^3) NO_2 may lead to sudden death. More characteristic is insidious, delayed pulmonary edema within hours. Finally, delayed inflammatory changes may lead to death hours or days after exposure (Plog, 1988).

A few accidental exposure studies estimated the NO_2 concentration leading to signs and symptoms of toxicity. Norwood *et al*. (1966) reported pulmonary edema in a worker who had a 30-minute exposure to NO_2 in an oxyacetylation cutting process. Recreation of the exposure conditions produced an NO_2 concentration of up to 90 ppm.

In another accidental human exposure, 3 astronauts inhaled a high concentration of NO_2 for 4 minutes and 40 seconds during reentry before the air was cleared inside the cabin (Hatton *et al*., 1977). Postflight analysis suggested a peak cabin concentration of 750 ppm (1,530 mg/m^3) at 1 atm, and an average exposure to 250 ppm (510 mg/m^3). One hour after splashdown, the astronauts complained of tightness of the chest, retrosternal burning sensation, inability to inhale deeply, and a nonproductive cough. The following day, the astronauts were unable to hold their breath or perform the forced expiratory maneuvers required for pulmonary function tests (PFTs). Chest x-rays were normal on the day of exposure but on the following day the blood gases and chest x-rays were consistent with diffuse chemical pneumonitis. Recovery occurred over several days; chest roentgenograms appeared normal by the fifth day after overexposure.

In an early attempt at controlled exposure to high NO_2 concentrations, Adley (1946) reported that exposure of an unspecified number of workmen to an average concentration of 80 ppm (150 mg/m^3) NO_2 for 4 minutes produced slight tightness of the chest. However, 4-minute exposure to an average concentration of 38 ppm (71 mg/m^3) resulted in no reports of symptoms. Exposure to an average concentration of 210 to 352 ppm for about 3 minutes resulted in a spontaneous, dry cough and tightness of the chest. A few hours after exposure, subjects reported general malaise.

In a human inhalation study by Meyers and Hine (1961), sensory responses were recorded for 7 or 8 normal volunteers exposed to 1, 5, 13, or 25 ppm NO_2 for 5 minutes each. Eye irritation and pulmonary discomfort were not significantly different from control values, but slight to moderate nasal irritation was noted at 13 ppm (7 of 8 subjects) and 25 ppm (5 of 7 subjects). Exposure to 50 ppm NO_2 produced symptoms of severe pulmonary distress in 1 of 7 subjects resulting in termination of exposure after only 1 minute. In a 1 hour inhalation study, exposure of 5 subjects to 10 ppm NO_2 resulted in pulmonary discomfort, characterized as pharyngeal irritation in all subjects and slight to moderate nasal irritation in 3 subjects. Eye irritation was not significantly

different from control values and no consistent changes in inspiratory reserve, expiratory reserve, or vital capacity were observed.

Nakamura (1964) exposed 13 healthy young adult volunteers to specific concentrations of NO_2 ranging from 3 to 40 ppm for 5 minutes. Two volunteers were exposed twice at different concentrations. Although airway resistance increased following exposure, no significant dose-response relationship between NO_2 concentration and increased airway resistance was observed. Subjective complaints were concentration-dependent and included bad odor, irritation of the upper airway, coughing, and unusual feeling in the lungs.

Yokoyama (1968) exposed up to 8 healthy subjects, 5 of whom were smokers, to NO_2 concentrations of 2.7, 6.2, 12.6, and 16.9 ppm for 10 minutes via mouthpiece. An average increase in pulmonary flow resistance was significant only at 16.9 ppm. The average 22% increase at this concentration occurred at the end of exposure and the highest individual increase in resistance was 78%. Other pulmonary function tests remained unchanged at all exposure levels. Irritation in the throat was noted in only 1 of 8 subjects exposed to 16.9 ppm.

Exposure of normal volunteers to 5 and 7.5 ppm NO_2 has been performed (von Nieding and Wagner, 1977; von Nieding and Wagner, 1979; von Nieding *et al*., 1973; Beil and Ulmer, 1976). However, these studies lacked details, both of methods and of results, which makes evaluation difficult. In the best of these studies, Von Nieding and Wagner (1977) exposed 11 healthy male volunteers in a chamber to 5 ppm NO_2 with light intermittent exercise. After 2 hours of exposure, a statistically significant 60% increase in total airway resistance (R_T) was observed relative to the pre-exposure R_T. The mean arterial oxygen partial pressure (PaO_2) decreased significantly from 89.6 to 81.6 mm Hg. R_T remained significantly elevated 1 hour following exposure while PaO_2 returned to normal. Pulmonary function data for individual subjects and subjective symptoms were not reported.

In 18 normal nonsmoking subjects exposed to filtered air or 2 ppm (4 mg/m^3) NO_2 for 1 hour (Mohsenin, 1988), airway reactivity to methacholine challenge increased significantly after NO_2 exposure. However, no significant changes were noted in lung volumes, flow rates, or respiratory symptoms.

In controlled studies, exposure of asthmatics to up to 4 ppm NO_2 have not resulted in statistically significant changes in PFTs (Koenig *et al*., 1988; Linn *et al*., 1985a; Linn *et al*., 1986). Exposure of subjects with chronic obstructive pulmonary disease to concentrations up to 3 ppm NO_2 have resulted in no changes (Linn *et al*., 1985b) or marginal to equivocal changes in PFTs (Morrow and Utell, 1989).

Controlled acute exposure studies with asthmatics show an increase in airway reactivity in response to NO_2 concentrations between 0.25 and 0.50 ppm (0.47 and 0.9 mg/m^3). Bauer *et al*. (1986) reported that NO_2 potentiated exercise-induced bronchospasm and airway reactivity to cold air provocation in asthmatics following exposure to 0.3 ppm (0.6 mg/m^3) for 30 minutes. Exposure to NO_2 while at rest resulted in no significant change in pulmonary function. Following 10 minutes of exercise, significant reductions in FEV_1 ($p<0.01$) and partial expiratory flow rates at

60% of total lung capacity were observed. One hour after NO_2 exposure and exercise, pulmonary function returned to baseline. Mohsenin (1987) reported an increase in airway reactivity in normal subjects following exposure to 0.5 ppm (0.9 mg/m^3) NO_2 for 1 hour. Other studies have reported the absence of airway reactivity in asthmatics at these concentrations (Rubinstein *et al*., 1990; Avol *et al*., 1988; Roger *et al*., 1990).

Additional controlled-exposure studies of asthmatics demonstrate an increase in nonspecific airway reactivity following exposure at or below 0.25 ppm (0.47 mg/m^3) NO_2. Jorres *et al*. (1990) report an increase in airway reactivity to hyperventilation of 0.75 ppm SO_2 without altering airway tone following exposure to 0.25 ppm NO_2 for 30 minutes. Kleinman *et al*. (1983) report an increase in airway reactivity in 2/3 of 31 subjects exposed to 0.2 ppm (0.4 mg/m^3) NO_2 for two hours. Orehek *et al*. (1976) report increased airway reactivity in 13 of 20 subjects exposed to 0.1 ppm (0.2 mg/m^3) for one hour. Other investigators report no increase in airway reactivity in asthmatics following NO_2 exposure at or below 0.25 ppm (0.47 mg/m^3) (Hazucha *et al*., 1983; Jorres *et al*., 1991). Results from these studies suggest that a sensitive subgroup of asthmatics with increased airway reactivity following inhalation exposure to NO_2 may be present in the general population, and that they contribute to the wide range of responsiveness present among asthmatics to inhaled NO_2 (Utell, 1989).

Predisposing Conditions for Nitrogen Dioxide Toxicity

Medical: Persons with asthma and other preexisting pulmonary diseases, especially RADS, may be more sensitive to the effects of NO_2 (Reprotext, 1999).

Chemical: There is a theoretical possibility that persons who live in heavily polluted areas, who drink water with high levels of nitrate, or who are exposed to other oxides of nitrogen, nitrates, or nitrites may be more sensitive to NO_2 because of the potential induction of methemoglobinemia (Reprotext , 1999). However, there is no empirical evidence of this effect.

V. Acute Toxicity to Laboratory Animals

Although accurate quantitative data are lacking for life-threatening exposures to NO_2 in humans, the clinical syndrome in accidental human exposure cases is similar to that seen in experimental animals exposed to high levels of NO_2 (Mauderly, 1984). The most comprehensive acute lethality study for NO_2 in experimental animals was done by Hine *et al*. (1970). Numerous exposure durations, ranging from 5 minutes to 24 hours, were examined for each concentration of NO_2, which ranged from 5 ppm to 250 ppm, in mice, rats, guinea pigs, rabbits, and dogs. At low levels of exposure up to 20 ppm, signs of irritation were minimal, and no effects on behavior were noted. At 40 ppm and above, signs of toxicity included eye irritation, lacrimation, and increased respiration followed by labored breathing. In all 5 species, 50 ppm was considered a critical concentration, below which mortality rarely occurred with exposures up to 8 hours. In animals which developed pulmonary edema there was profuse, occasionally hemorrhagic fluid discharge from the nares. Gross pathology revealed mottled, fluid-filled lungs. Some guinea pigs exhibited sudden exaggerated gasping for air, then convulsed and died. Pulmonary edema was not present

in these animals but the vocal cords were slightly edematous, which suggested asphyxiation due to laryngeal spasm.

Because the mortality data in Hine *et al*. (1970) were not presented in conventional form by the standard LC_{50} method (the study varied exposure duration for a given concentration), the data were normalized to a 1-hour exposure using Haber's equation ($C^n \times T = K$). The exponent "n" was determined for each species by varying the term n in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. Only exposure durations which reasonably bracketed 1 hour 20 minutes to 4 hours in length were used in the probit analysis. Exposure durations outside of this range tended to deviate from Haber's formula. The term was subsequently found to be between 3.0 and 4.0 for mice, guinea pigs, and dogs. These estimates of the exponent "n" are similar to the exponent value (n = 3.5) estimated by ten Berge *et al*. (1986) using the same data set. The data sets for rats and rabbits were heterogeneous or too weak for "n" determination.

Acute lethality determinations for the LC_{50}, maximum likelihood estimate corresponding to 5% mortality (MLE_{05}), and benchmark doses at the lower 95% confidence interval expected to produce a response rate of 5% and 1% (BC_{05} and BC_{01}, respectively) for mice, rats, guinea pigs and dogs are shown in Table 1.

Table 1. Nitrogen Dioxide Acute Lethality Determinations (in ppm) Derived from the Data by Hine *et al*. (1970) and Normalized to 1-Hour Exposure.

Species	LC_{50}	MLE_{05}	BC_{05}	BC_{01}
Mouse	93	70	59	50
Rat[1]	106	60	47	34
Guinea Pig	83	44	28	18
Dog	125	96	62	48

[1] Only 1 hour exposure duration data were used to derive the rat lethality values.

In other lethality studies, Carson *et al*. (1962) observed 5-, 15-, 30-, and 60-minute LC_{50}'s of 416, 201, 162, and 115 ppm, respectively, in young male rats. A 15-minute LC_{50} of 315 ppm was observed in rabbits. Higgins *et al*. (1972) determined a 5 minute LC_{50} of 831 and 1,880 ppm in rats and mice, respectively. Hilado and Machado (1977) observed a 10-minute LC_{50} of about 1,000 ppm in male mice. Takenaka *et al*. (1983) determined 16 hour LC_{50}'s in 9 strains of mice and 4 strains of rats. In mice, the LC_{50}'s ranged from 67 ppm to 33 ppm. In rats, the LC_{50}'s ranged from 56 ppm to 39 ppm. Takenaka *et al*. (1983) also observed a 16 hour LC_{50} of 22 ppm (males) and 28 ppm (females) in Golden hamsters, and 62 ppm (males) and 50 ppm (females) in Hartley guinea pigs.

Steadman *et al*. (1966) exposed groups of rats, guinea pigs, rabbits, squirrel monkeys, and beagle dogs to NO_2 concentrations of 123 mg/m³ (65 ppm) and 67 mg/m³ (36 ppm) for 8 hours or more.

Signs of eye and nose irritation were noted in all animals during the first hour of exposure to 123 mg/m^3, accompanied by anorexia and lethargy. Monkeys were the most susceptible to the lethal effects of NO_2, with 3 out of 3 dying at each exposure level within the first 6.5 hours.

Henry and co-workers (1969) reported that monkeys exposed to 35-50 ppm NO_2 for 2 hours showed a marked decrease in resistance to infection when subsequently challenged with *Klebsiella pneumoniae*. Animal studies indicate that decreased host resistance to infection is influenced more by concentration of NO_2 than by duration of exposure (CARB, 1985).

Lung-only exposure of sheep to 500 ppm NO_2 for 15-20 minutes resulted in an immediate tidal volume decrease and an increase in both breathing rate and minute volume (Januskiewicz and Mayorga, 1994). Maximal lung resistance and dynamic lung compliance changes occurred at 24 hours post-exposure. Histopathologic examination of lung tissue revealed patchy edema, mild hemorrhage, and polymorphonuclear and mononuclear leukocyte infiltration. Signs of NO_2-induced toxicity were significantly attenuated when sheep were exposed to 100 ppm (Januskiewicz *et al*., 1992), or to 500 ppm through a face mask (nose-only exposure) (Januskiewicz and Mayorga, 1994).

Species-specific sensitivity to NO_2 inhalation may exist, based, in part, on animal size or weight-specific minute ventilation (Book, 1982; Carson *et al*., 1962; Januskiewicz and Mayorga, 1994). The evidence indicates that smaller experimental animals species, such as rodents, are more susceptible to the toxic effects of NO_2 than larger animals such as dogs, sheep, and humans (Book, 1982; Januskiewicz and Mayorga, 1994).

VI. Reproductive or Developmental Toxicity

Limited data are available on the effects of NO_2 on reproduction. Reproductive studies in animals have been done but are difficult to interpret. In one study, exposure of pregnant rats to 0.43, 0.045, or 0.018 ppm (0.81, 0.085, or 0.034 mg/m^3) NO_2 resulted in an increase in intrauterine deaths, stillbirths, and certain unspecified developmental abnormalities, and in decreased birth weights (Gofmekler *et al*., 1977); the original reference was not available for review. Tabacova *et al*. (1985) found dose-dependent neurobehavioral deviations and delays in eye opening and incisor eruption in the offspring of rats exposed to 0.5 ppm (0.9 mg/m^3) NO_2 and higher. The authors suggest that the effects may be due to lipid peroxidation of the placenta. No effects in spermatogenesis, germinal cells, or interstitial testicular cells occurred in rats exposed to 1.0 ppm (2 mg/m^3) NO_2 for 7 hours/day, 5 days per week, for 3 weeks (Kripke and Sherwin, 1984). No human reproductive studies of NO_2 were available at the time of this review.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 0.25 ppm (470 μg/m³)
(California Ambient Air Quality Standard)

Study	California Air Resources Board (CARB), 1992
Study population	sensitive humans (asthmatics)
Exposure method	inhalation
Critical effects	increase in airway reactivity
LOAEL	
NOAEL	0.25 ppm
Exposure duration	1 hour
Extrapolated 1 hour concentration	0.25 ppm
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	0.25 ppm (0.47 mg/m³; 470 μg/m³)

The REL is the California Ambient Air Quality Standard.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the procedures.

The few studies that observed disabling effects on pulmonary function following NO_2 exposure did not provide reliable values. Meyers and Hine (1961) observed respiratory distress in 1 of 7 test subjects exposed to 50 ppm for 1 minute. However, this exposure is too short for consideration of a severe adverse effect level. Likewise, the disabling effects produced by accidental exposure of astronauts to high concentrations of NO_2 were too variable and too short for consideration. Hine *et al*. (1970) observed signs of compromised lung function in 5 experimental animal species exposed to greater than 40-50 ppm. However, extrapolation of the animal NOAEL (40-50 ppm) to sensitive humans using a total uncertainty factor of 100 would result in a severe adverse effect level significantly below 4 ppm. This concentration of NO_2 failed to produce symptoms of mild irritation in asthmatic subjects (Linn *et al*., 1985a).

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the procedures.

Applying an uncertainty factor of 30 (3 to account for interspecies differences and 10 for increased susceptibility of sensitive human individuals) to the BC_{05}'s from Table 1 results in a life-threatening level of 1-2 ppm, for 1-hour exposure to NO_2. Probit analysis to determine the BC_{05} from rat lethality data by Higgins *et al*. (1972) and mouse lethality data by Hilado and Machado

(1977) also resulted in a life-threatening level of 2 ppm following adjustment of the BC_{05}'s to 1-hour exposure and application of appropriate uncertainty factors. While the benchmark dose results of 3 lethality studies in a total of 4 different experimental animal species are consistent, they result in a life-threatening level value (2 ppm) that is known to cause no symptoms of irritation or changes in pulmonary function in sensitive humans (Linn *et al*., 1985a; Linn *et al*., 1985b). Species-specific susceptibility comparisons of experimental animals suggest that humans are less sensitive to the toxic effects of NO_2 than smaller experimental animal species (Book, 1982; Januskiewicz and Mayorga, 1994). However, Steadman *et al*. (1966) observed that squirrel monkeys were more susceptible to the acute lethal effects of NO_2 than rodents. Until this issue can be resolved, these derivations are meant for illustrative purposes only.

NIOSH (1995) lists a (revised) IDLH for nitrogen dioxide of 20 ppm based on acute inhalation toxicity data in humans. NIOSH states that this may be a conservative value due to the lack of relevant acute toxicity data for workers exposed to concentrations above 20 ppm.

VIII. References

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